201-14889

COURTNEY M. PRICE
VICE PRESIDENT
CHEMSTAR

American Chemistry Council Good Chemistry Makes It Possible

December 10, 2003

By Mail
Mike Leavitt, Administrator
U.S. EPA
PO Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program – Test Plan Submission from HERTG
Registration Number

Dear Administrator Leavitt:

The American Chemistry Council Petroleum Additives Panel Health, Environmental, and Regulatory Task Group (HERTG) submits for review and public comment its test plan report, as well as related robust summaries, for the single chemical, Methylcyclopentadienyl Manganese Tricarbonyl, MMT® (CAS #12108-13-3), under the Environmental Protection Agency's High Production Volume (HPV) Chemical Challenge Program. The HERTG understands that there will be a 120-day review period for the test plan report and that all comments generated by or provided to EPA will be forwarded to the HERTG for consideration.

Thank you in advance for your attention to this matter. If you have any questions regarding the test plan report or the robust summaries, or HERTG's activities associated with the Challenge Program, please contact Sarah McLallen at 703-741-5607 (telephone), 703-741-6091 (telefax) or Sarah_McLallen@americanchemistry.com (e-mail).

Sincerely yours,

cc: HERTG members

HIGH PRODUCTION VOLUME (HPV)

CHALLENGE PROGRAM

TEST PLAN

For

Methylcyclopentadienyl Manganese Tricarbonyl
(MMT®)

Prepared by
The American Chemistry Council
Petroleum Additives Panel
Health, Environmental, and Regulatory Task Group

December 2003

LIST OF MEMBER COMPANIES IN THE
HEALTH, ENVIRONMENTAL AND REGULATORY TASK GROUP

The Health, Environmental, and Regulatory Task Group (HERTG) of the American Chemistry Council Petroleum Additives Panel includes the following member companies:

Chevron Oronite Company, LLC

Crompton Corporation

Ethyl Corporation

ExxonMobil Chemical Company

Ferro Corporation

Groupe SNPE

Infineum

The Lubrizol Corporation

Rhein Chemie Corporation

Rhodia, Inc.

1.0 INTRODUCTION

In March 1999, the American Chemistry Council (formerly the Chemical Manufacturers Association) Petroleum Additives Panel Health, Environmental, and Regulatory Task Group (HERTG), and its participating member companies committed to participate in the Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program for certain chemicals. This test plan follows up on that commitment. Specifically, this test plan sets forth how the HERTG intends to address the relevant endpoints for the following substance- Methylcyclopentadienyl Manganese Tricarbonyl (CAS No.: 12108-13-3)

In preparing this test plan the following steps were undertaken:

Step 1: A review of the literature and confidential company data was conducted on the physicochemcial properties, mammalian toxicity endpoints, and environmental fate and effects for Methylcyclopentadienyl Manganese Tricarbonyl (CAS No.: 12108-13-3) using its CAS number, CAS name, and synonyms. Searches included the following sources: MEDLINE, BIOSIS, CANCERLIT, CAPLUS, CHEMLIST, EMBASE, HSDB, RTECS, EMIC, and TOXLINE databases; the TSCATS database for relevant unpublished studies on these chemicals; and standard handbooks and databases (e.g., Sax, CRC Handbook on Chemicals, IUCLID, Merck Index, and other references) for physicochemical properties.

Step 2: The compiled data was evaluated for adequacy in accordance with the EPA guidance documentation.

2.0 GENERAL SUBSTANCE INFORMATION

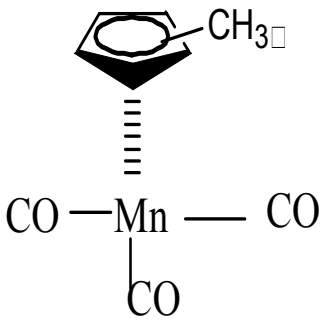
The substance that is the subject of this test plan is used as a petroleum additive in petroleum base stocks. The chemical name, CAS Registry Number, molecular weight and chemical structure for this substance are presented below.

Chemical Name: **Methylcyclopentadienyl Manganese Tricarbonyl (**MMT)

Chemical Abstract Service Registry Number: 12108-13-3

Molecular Weight: 218.1

Chemical Structure:



12108-13-3

3.0 EXPOSURE INFORMATION

Manufacture

Methylcyclopentadienyl Manganese Tricarbonyl (MMT) is manufactured at a plant that is under a toll manufacturing agreement with a member of the HERTG.

The manufacturing process entails the following. Under a nitrogen atmosphere, methylcyclopentadienyl dimer is added to a dispersion of sodium metal in diethylene glycol dimethyl ether. A constant elevated reaction temperature is maintained to yield sodium-methylcyclopentadienyl, an intermediate in the reaction process. Manganese chloride is then added to the stirred mixture containing the sodium – methylcyclopendienyl intermediate. An elevated temperature is maintained during the addition. Upon completion, the reaction gives bis(methylcyclopentadienyl)manganese, the second intermediate of the reaction process. The reaction vessel is then pressurized with carbon monoxide. The addition of carbon monoxide results in MMT which is separated from the reaction mixture via vacuum distillation.

Use

MMT is a fuel additive that boosts gasoline octane and improves combustion. MMT also helps lower tailpipe emissions of NOx and reduce refinery emissions of nitrous oxide. Both emissions are so called "green house gasses" that may be linked to global warming.

Distribution

MMT is shipped in specially designed containers that are engineered to withstand pressure, dropping and the rigors associated with transportation. At the customer's site the product is transferred from the transportation container to bulk storage tanks. The transfer is accomplished under a nitrogen atmosphere designed to reduce the potential for vapors to be released to the environment. Empty transportation containers are returned. From the storage tank, customers blend MMT into fuel using dedicated metering pumps designed to add the desired quantities. Typically, only 10 to 40 PPM of manganese is added to gasoline; thus MMT is very dilute in gasoline. Gasoline with and without MMT has the same toxicity, i.e., the MMT is such a dilute component of the fuel it presents no health issues beyond that of the gasoline itself. Gasoline

containing MMT requires no special handling and customers distribute it through normal operating procedures.

Safe product handling is promoted through on-site training sessions, videos, and manuals. A transportation driver's manual, an occupational handling manual, and medical guide detail practices and emergency procedures should an accident occur.

Workers involved in MMT manufacture are a potentially exposed population. However, monitoring at the manufacturing site has revealed no exposure issues. Other populations potentially exposed to MMT are personnel involved in the transport, off-loading and blending of MMT into fuel. The safety engineering of the transportation containers, the fact that off-loading is accomplished under a nitrogen atmosphere designed to reduce the potential for vapors to be released to the environment, and the slow metering of the additive into fuel to achieve the very dilute concentration greatly diminish the possibly of exposure. Auto mechanics and consumers fueling their vehicles are potentially another exposed population.

If exposure were to occur, the most likely routes would be skin absorption, inhalation, and contact with the eye. Protective clothing, face shields, and engineering controls that are part of the safe handling training minimize the likelihood of occupational exposures. Harmful exposure of the general population to MMT is not reasonably expected to occur due to the very dilute concentration of the additive.

4.0 PHYSICOCHEMICAL PROPERTIES

4.1 Summary of Available Data
MMT has a boiling point of 231.67 ^{o}C and a vapor pressure of 0.05 mm Hg @ 20ºC.

4.2 Data Assessment and Test Plan for Physicochemical Properties Relevant to Environmental Fate
The water solubility at 20ºC is 29 mg/L. The octanol/water partition coefficient Log Kow=3.7. MMT is a liquid and, therefore, the melting point is not applicable.

5.0 ENVIRONMENTAL FATE DATA

5.1 Biodegradability

5.1.1 Summary of Available Data
An OECD 301 D was conducted on MMT which showed that the chemical is not readily biodegradeable.
5.1.2 Data Assessment and Test Plan for Biodegradability
The available biodegradability data are adequate and reliable. No additional biodegradability tests of MMT will be conducted.

5.2 Hydrolysis

5.2.1 Summary of Available Data

No published or unpublished hydrolysis studies of MMT were located.

5.2.2 Data Assessment and Test Plan for Hydrolysis

The potential for MMT to hydrolyze will be characterized in a technical discussion.

5.3 Photodegradation

5.3.1 Summary of Available Data

Photochemical decomposition study was conducted on MMT. The half-life in mid day sunlight ~1 minute, disappearance quantum yield is 0.13

5.3.2 Data Assessment and Test Plan for Photodegradation

The available photodegradation data are adequate and reliable. No further testing will be conducted on MMT.

5.4 Fugacity Modeling

5.4.1 Summary of Available Data

There are no published or unpublished fugacity-based multimedia fate modeling data for MMT.

5.4.2 Test Plan for Fugacity

The relative distribution of MMT among environmental compartments will be evaluated using Level I Fugacity modeling.

Input data to run the EQC Level I model will require an additional computer model to estimate physical/chemical properties from a structure. The model used for this purpose will be EPIWIN, version 3.02[1], which was developed by the Syracuse Research Corporation. EPIWIN includes algorithms for estimating all physical and chemical properties needed for the EQC model.

6.0 ECOTOXICOLOGY DATA

6.1 Aquatic Ecotoxicity Testing

6.1.1 Summary of Available Data

The 48 hour EC_{50} of MMT determined in *Daphnia* is 0.83 mg/L. Reliable aquatic ecotoxicity data for fish and reliable aquatic ecotoxicity data algae are not available.

6.1.2 Data Assessment and Test Plan for Acute Aquatic Ecotoxicity

[1] Environmental Science Center- Syracuse Research Corporation- EPI for windows.

The available acute aquatic toxicity data in *Daphnia* and fish are adequate and reliable. Additional testing will be performed in algae according to OECD Test Guideline 203.

7.0 MAMMALIAN TOXICOLOGY DATA

7.1 Acute Mammalian Toxicity

7.1.1 Summary of Available Data

Several acute oral and dermal toxicity studies and an acute inhalation toxicity study are available for MMT. In these studies, the oral LD_{50} ranged from 58 to 175 mg/kg and the dermal LD_{50} ranged from 140-795 mg/kg. The 1 and 4 hour LC_{50}s in male rats were 0.247 and 0.076 mg/L, respectively.

7.1.2 Data Assessment and Test Plan for Acute Mammalian Toxicity

Adequate and reliable acute oral, dermal and inhalation toxicity tests were performed for MMT. Additional acute mammalian toxicity testing will not be conducted.

7.2. Mutagenicity

7.2.1 Summary of Mutagenicity Data

A negative *Salmonella typhimurium* point mutation assay is available for MMT. In Chinese Hamster Ovary cells, in the presence of metabolic activation, MMT induced structural chromosomal aberration. Without metabolic activation, MMT failed to induce a significant increase in chromosomal aberrations.[2] An in vivo mouse micronucleous test did not demonstrate any chromosome aberration effects.

7.2.2 Data Assessment and Test Plan for Mutagenicity Toxicity

An adequate and reliable *Salmonella typhimurium* point mutation assay and chromosomal aberration test are available for MMT. No further testing will be conducted.

7.3 Repeated-dose, Reproductive and Developmental Toxicity

7.3.1 Summary of Repeated-Dose Toxicity, Reproductive and Developmental Toxicity Data

A 14-week repeat exposure inhalation toxicity study in male and female rats and mice and in male primates and a developmental toxicity study in rats are available on MMT. The no observed adverse effect level in the 14-week inhalation study was 0.3 ug/L. MMT did not exhibit developmental toxicity at dose levels up to and including 9 mg/kg/day (gestation days 6-15).

No published or unpublished reproductive toxicity studies on MMT were located; however, the 14 week repeat exposure inhalation study conducted in rats, mice and primates included the microscopic evaluation of both male and female rat and mouse and male primate reproductive

[2] Blakey and Bayley, Environmental Molecular Mutagenesis."Induction of Chromosomal Aberrations by the Fuel Additive MMT in Chinese Hamster Ovary Cells". 1995, 25.

organs. No reproductive toxicity was observed at the high exposure level (30.2 ug/L) in any species. This study satisfies both repeat dose toxicity and reproductive toxicity for HPV purposes.

7.3.2 Data Assessment and Test Plan for Repeated-dose Toxicity

An adequate and reliable 14-week repeat exposure inhalation toxicity study on rats, mice and primates and an adequate and reliable developmental toxicity study in rats are available on MMT. The repeat exposure study meets the HPV program for both repeat dose toxicity and reproductive toxicity. No additional repeat dose, reproductive or developmental toxicity testing will be conducted.

8.0 SUMMARY

The following table summarizes the available data and proposed testing on MMT.

Table 1
Summary Table of Available Data and Proposed Testing on
Methylcyclopentadienyl Manganese Tricarbonyl

CAS No.: 12108-13-3	Study Results	Testing Proposed
Physical/Chemical Characteristics		
Melting Point	Liquid	Not applicable
Boiling Point	231.67 ^{o}C	No
Vapor Pressure	0.05 mm HG @ 20ºC	No
Water Solubility	29 mg/L	No
Partition Coefficient	3.7	No
Environmental Fate		
Biodegradation	Not readily biodegradeable	No
Hydrolysis	No Data Located	Technical Discussion
Photodegradation	Half-life in midday sunlight~1 minute	No
Fugacity	No Data Located	Yes
Ecotoxicity		
Acute Toxicity to Fish	No Data Located	Yes
Acute Toxicity to Invertebrates	Daphnia 48 Hr EC50: 0.83 mg/L	No
Acute Toxicity to Algae	No Data Located	Yes
Mammalian Toxicity		
Acute Toxicity	Oral LD50: 58-175 mg/kg (rat) Dermal LD50: 140-795 mg/kg (rabbit) Inhalation 1 Hour LC50: 0.247 mg/L (rat) Inhalation 4 Hour LC50: 0.076 mg/L (rat)	No
Repeated Dose Toxicity	14 Week Inhalation NOAEL: 0.3 ug/L (rat)	No
Developmental Toxicity	NOEL: 9 mg/kg/day (gestation days 6-15)	No
Reproductive Toxicity	14 Week Inhalation Study-Reproductive Toxicity NOEL: 30.2 ug/L	No
Genotoxicity		
Gene Mutation	Negative	No
Chromosomal Aberration	in vitro CHO without activation-positive; In vitro CHO with activation and in vivo in mouse-negative	No

201-14889A

Substance: **Methylcyclopentadienyl manganese tricarbonyl (MMT®)**

Summary prepared by: **Petroleum Additives Panel**
Health & Environmental Research Task Group

1. General Information

Physico-chemical Data

Boiling Point

Test Substance	
CAS #	CAS# 12108-13-3
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Parameter	Boiling Point
Literature Cited Data	231.67 ^{o}C
References	ACGIH 1980; EPA Chemical Profile 2003
Other	Updated: 8/22/2003

Vapor Pressure

Test Substance	
CAS #	CAS# 12108-13-3
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Parameter	Vapor Pressure
Literature Cited Data	7.3 mm Hg at 100 ^{o}C
References	ACGIH 1980; EPA Chemical Profile 2003
Other	Updated: 8/22/2003

Water Solubility

Test Substance	
CAS #	CAS# 12108-13-3
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Parameter	Water Solubility
Literature Cited Data	29 mg/L @ 25^{o}C (Determined according to EPA Chemical Fates Test Guidelines, EPA 560/6-82-003)
References	Garrison, A. *et al*., Environmental Fate of Methylcyclopentadienyl Manganese Tricarbonyl, Environmental Toxicology and Chemistry, Vol. 14, No. 11, pp.1859-1864 (1995).
Other	Updated: 10/9/2003

Partition Coefficient

Test Substance	
CAS #	CAS# 12108-13-3
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Parameter	Partition Coefficient
Literature Cited Data	Log K_{ow} = 3.7 (Determined according to EPA Chemical Fates Test Guidelines, EPA 560/6-82-003)
References	Garrison, A. *et al*., Environmental Fate of Methylcyclopentadienyl Manganese Tricarbonyl, Environmental Toxicology and Chemistry, Vol. 14, No. 11, pp.1859-1864 (1995).
Other	Updated: 10/9/2003

Photodegradation

CAS No.	CAS# 12108-13-3
Test Substance Name	Methylcyclopentadienyl manganese tricarbonyl
GLP (Y/N)	Not Specified
Year Published	1995
Remarks for Test Conditions	Photolysis experiments were conducted in deionized, reverse osmosis purified water of initial pH 6.5. The pH was measured after the addition of KCL to increase the ionic strength of the water. The reaction vessels used were 16 x 125 mm borosilicate screw cap culture tubes with aluminum foil-faced butyl septa. The test material was added directly to the water to obtain a nominal 1 mg/L solution. Both natural midday sunlight and a solar simulator were used as radiation sources. Sample temperature was maintained at $25 \pm 2^{o}C$. Samples were irradiated for specific time intervals and then placed in the dark in a refrigerator until an entire run was completed, at which time all samples from the run were analyzed. The photolysis rate constant was calculated from the first order integrated rate equation: Ln $C_t = -kt + ln\ C_o$, where C_t is the test material concentration at time t and C_o is the initial concentration. Least square regression analysis was used for the rate constant (k) calculation. The concentration of the test material in the sample solutions was determined by GC-MS. Reaction products were identified by GC-MS, GC-FTIR infrared spectroscopy and X-ray diffraction.
Results	The test material photolyzed rapidly in deionized water exposed to January midday sunlight in Athens Georgia. The disappearance of the test material followed first order kinetics, with a calculated half-life of 0.93 minutes. The rate constant was $0.74 \pm 0.01\ min^{-1}$. Reaction products were identified as methylcyclopentadiene, cyclopentadiene and carbon monoxide and a manganese carbonyl that readily oxidized to trimanganese tetroxide.
Conclusions	The disappearance of the test material followed first order kinetics, with a calculated half-life of 0.93 minutes. The rate constant was $0.74 \pm 0.01\ min^{-1}$. Reaction products were methylcyclopentadiene, cyclopentadiene and carbon monoxide and a manganese carbonyl that readily oxidized to trimanganese tetroxide.
Data Quality	Reliable without restriction (Klimisch Code)
References	Garrison, A. *et al*., Environmental Fate of Methylcyclopentadienyl Manganese Tricarbonyl, Environmental Toxicology and Chemistry, Vol. 14, No. 11, pp.1859-1864 (1995).
Other	Updated: 10/9/2003

Biodegradation

Test Substance	
CAS #	CAS# 12108-13-3
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Remarks	Test material purity: 98.2%
Method	
Method/Guideline Followed	OECD 301D, Ready Biodegradability Closed Bottle Test
Test Type (aerobic/anaerobic)	Aerobic
GLP (Y/N)	Y
Year (study performed)	1990
Contact time (units)	28 days
Test apparatus	*32 standard 300 mL BOD bottles containing test and reference materials and control bottles. Bottles were incubated in a water bath at 20°C in the dark.*
Inoculum	The inoculum was secondary effluent collected from a domestic wastewater treatment plant. The effluent was filtered through coarse filter paper and the first 200 mL were discarded. The remaining filtered effluent was aerated at room temperature until used.
Test medium:	*The aqueous medium provided essential nutrients and trace elements necessary to sustain the inoculum throughout the testing period.*
Cultures/replicates:	*Two replicate test cultures, two replicate blank control cultures and two reference control cultures per evaluation interval.*
Temperature of incubation:	20°C
Dosing procedure:	Three liters of aqueous nutrient media were spiked with 9 ul of test material to obtain a concentration of 2 mg C/L.
Study initiation:	Four, 4-liter glass bottles were each filled to the 1 liter mark with deionized water. Three mL of test media were added to each bottle. In addition the positive control bottle received 977 ul of Aniline and the "test bottle" received 9 ul of the test material. These two bottles were then inoculated with three drops of aerated secondary effluent. The third bottle (control+inoculum) received three drops of effluent and the fourth bottle (control only) did not receive test material, positive control or microbial inoculum. All bottles were then filled to the 3-liter mark with deionized water. Since the test material did not visibly dissolve in the media, this bottle was covered with aluminum foil and placed in a sonicator for 10 minutes. Samples for GLC-FID analysis were taken from all bottles. Each solution was then transferred immediately into the respective BOD bottles. Bottles were sealed, covered with aluminum foil, and placed in a water bath in the dark at 20°C for incubation.
BOD Analysis	Immediately after preparation, duplicate bottles from each test system were analyzed for BOD using a Nester Model 8500 Dissolved Oxygen Monitor. Duplicate samples were analyzed for dissolved oxygen at time 0 and on days 5, 15 and 28.

GLC-FID analysis	The concentration of the test material in test dilution water was determined at day 0 using a Varian 3700 gas-liquid chromatography equipped with flame ionization detection. Calculations of test material concentration were performed using an external standard analysis. Concentrations of the test material in the samples were calculated based on a standard curve.
Controls:	Blank and positive controls used per guideline. Positive control was Aniline. A 2 mg C/L stock solution was prepared.
Method of calculating biodegradation values:	Percent biodegradation calculated as a function of the oxygen consumption in the test system as compared to the control.
Results	GLC results of day 0 test material analysis indicated that approximately 60% of the applied test material dose was in solution (2.4 mg/L), while the other 40% did not dissolve. Study results were corrected for the actual amount of test material in solution. More than 90% of the positive control applied dose was biodegraded in the 28-day test period. This verified that the microbial inoculum was viable and active. Approximately 46% of the test material in solution was biodegraded. Biodegradation appeared to have ceased between day 15 and 28. Since the measured BOD was not greater than 60% of the TOD, the test material was not readily biodegradable under these test conditions. The uninoculated and inoculated blanks met the appropriate acceptance criteria.
Degradation %	Test substance: 46 % in 28 days Positive control substance: 90.3 % in 28 days
Conclusions	The test substance was not readily biodegradable.
Data Quality	Reliable without restriction. (Klimisch Code)
References	Confidential business information
Other	Updated: 10/07/2003

2.0 AQUATIC ORGANISMS

2.1 Acute Toxicity to Aquatic Invertebrates (e.g. Daphnia)

Robust Summary 19-Daph-1

Test Substance	
CAS #	12108-13-3
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Remarks	Test Material Purity: 98.21%
Method	
Method/Guideline followed	Test protocol followed US EPA Toxic Substances Control Act Test Guideline #797.1300 (1985), Daphnid Acute Toxicity Test
Test Type	Static acute toxicity test
GLP (Y/N)	Y
Year (Study Performed)	1990
Species/Strain	*Daphnia magna*
Analytical Monitoring	Test material concentrations were determined by Gas-Liquid Chromatography at 0 and 48 hours.
Exposure Period (unit)	48 hours
Statistical methods	Statistical analysis of the survival data was performed using standard binomial and probit methods.
Remarks field for test conditions (fill as applicable)	Juvenile daphnids less than 24-hours old were produced from laboratory in-house culture. Individual test concentrations were prepared for each test level. A measured volume of test material was added to a measured volume of dilution water in a glass volumetric. The test solutions were then poured into the test vessels. Duplicate 250 ml glass beakers containing 200 ml of test solution were prepared at each concentration. Two range finding studies were conducted using ten Daphnia magna each. From these results five concentrations were selected for evaluation in the main study. Twenty daphnids, less than 24 hours old were distributed into each concentration (10 daphnids/replicate). Daphnids were not fed during exposure. Control test chambers were handled in an identical fashion. Daphnids were observed at 4, 24 and 48 hours for immobility and abnormal effects. Temperature, dissolved oxygen and pH were determined in the first replicate at time 0 and in the second replicate at 48 hours. Test vessels were covered during the study. Light cycles were maintained at 16-hour light per day with an intensity of 50 to 70 foot-candles. Test solutions were maintained at 20 $\pm$ 1 C.

Test Concentrations (Nominal)	Initial Range Finding Study: 0.001, 0.01, 0.10 and 1 mg/L Second Range Finding Study: 1.0 and 10 mg/L Definitive Study: 0.65, 1.3, 2.5, 5.0 and 10 mg/L
Results	48 hour EC_{50}=0.83 mg/L
Remarks	During the definitive study the analytical concentrations for the time 0 hour samples yielded an average of 56% of nominal. By 48 hours concentrations had decreased to an average of 28% of nominal. The mean measured concentrations for the study were 0.29, 0.65, 1.0, 2.0 and 3.5 mg/L. Fortification samples analyzed on each sampling day averaged 95% of recovery. All results were expressed based on mean measured analytical concentrations. Analytical determined exposure levels may have been lower than expected due to the photosensitivity and possible photodegradation of the test material. Immobility and surfacing were observed at all measured concentrations above 0.29 mg/L (0.65 to 3.5 mg/L). The 4, 24 and 48-hour EC50 values were 0.87, 0.94 and 0.83 mg/L. These were based on the observation of immobility and surfacing. The no effect concentration was 0.29 mg/L. Water chemistry: Dissolved oxygen: 7.5 – 8.2 mg/L (89 and 94% saturation at 22 and 20^{o}C); pH: 7.9 - 8.3
Conclusions	The 4, 24 and 48 hour EC50 values were 0.87, 0.94 and 0.83 mg/L.
Data Quality	Reliable without restriction (Klimisch Code)
References	Unpublished confidential business information
Other	Updated: 7/16/2003

3. Toxicity

3.1 Acute Toxicity

3.1.1 Acute Oral Toxicity

Robust Summary 19-Acute Oral -1
NOTE: 2 LD50 Robust Summaries Available On This Material

Test Substance	
CAS #	CAS# 12108-13-3
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Remarks	Test material dosed as received, purity not provided.
Method	
Method/Guideline followed	Similar to OECD 401
Test Type	Acute oral toxicity
GLP (Y/N)	N
Year (Study Performed)	1975
Species/Strain	Rats/ Sprague-Dawley strain
Sex	Male/Female
No. of animals/dose	5/sex
Vehicle	Corn oil
Route of administration	Oral (intragastric)
Dose level	40, 63, 100 and 158 mg/kg
Control group included	No
Range find study	Yes
Remarks field for test conditions	A single dose of the test material was administered intragastrically to five fasted male and female rats at each treatment level. The animals were observed for signs of toxicity frequently after dosing and daily thereafter for 14 days. Individual weights were recorded on the day of dosing and at termination. All animals were euthanized at the conclusion of the observation period. Gross necropsies were performed on all animals. The LD50 was calculated according to the method of Litchfield and Wilcoxon.
Results	LD50: 58 mg/kg (males and females) (37.4-89.9 mg/kg)
Remarks	Mortality was as follows: Dose Level (mg/kg) / Male Mortality / Female Mortality 40 / 0/5 / 4/5 63 / 0/5 / 3/5 100 / 4/5 / 4/5 158 / 4/5 / 5/5

	The test material appeared to be less toxic to males than to females. Those animals that survived to study termination exhibited the expected weight gain. Post dosing observations included salivation, weakness and diarrhea within 4 to 24 hours of dosing. The frequency of these observations was dose related. At necropsy residual test material was observed in the stomach and intestine of found dead animals. In some cases the test material appeared to discolor the adjacent viscera. No necropsy findings were noted in the animals that survived to study termination.
Conclusions	The test article, when administered to male and female Sprague-Dawley rats, had an acute oral LD50 of 58mg/kg (males and females) (37.4-89.9 mg/kg)
Data Quality	Reliable without restriction (Klimisch Code).
References	Unpublished confidential business information
Other	Updated: 7/21/2003

Robust Summary 19-Acute Oral –2

NOTE: 2 LD50 Robust Summaries Available On This Material

Test Substance	
CAS #	CAS# 12108-13-3
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Remarks	Test material dosed as received, purity not provided.
Method	
Method/Guideline followed	Similar to OECD 401
Test Type	Acute oral toxicity
GLP (Y/N)	N
Year (Study Performed)	1976
Species/Strain	Rats/ Sprague-Dawley strain
Sex	Male/Female
No. of animals/dose	5/sex
Vehicle	Corn oil
Route of administration	Oral (intragastric)
Dose level	126, 158, 200 and 251 mg/kg
Control group included	No
Range find study	Yes
Remarks field for test conditions	A single dose of the test material was administered intragastrically to five fasted male and female rats at each treatment level. The animals were observed for signs of toxicity immediately after dosing, at 4 hours and daily thereafter for 14 days. Individual weights were recorded on the day of dosing and at termination. All animals were euthanized at the conclusion of the observation period. Gross necropsies were performed on all animals. The LD50 was calculated according to the method of Litchfield and Wilcoxon.
Results	LD50: 175 mg/kg (males and females) (148-207mg/kg)
Remarks	Mortality was as follows: Dose Level (mg/kg) — Male Mortality — Female Mortality 126 — 0/5 — 1/5 158 — 2/5 — 2/5 200 — 4/5 — 3/5 251 — 5/5 — 5/5 All deaths occurred within three days of dosing. Those animals that survived to study termination exhibited the expected weight gain. All animals were lethargic 4 hours post dose administration. At necropsy residual test material was observed in the gastrointestinal tract of found dead animals. No necropsy findings were noted in the animals that survived to study termination.

Conclusions	The test article, when administered to male and female Sprague-Dawley rats, had an acute oral LD50 of 175 mg/kg (males and females) (148-207mg/kg).
Data Quality	Reliable without restriction (Klimisch Code).
References	Unpublished confidential business information
Other	Updated: 7/22/2003

3.1.2 Acute Inhalation Toxicity

Robust Summary 19-Acute Inhalation-1

Test Substance	
CAS #	*CAS#12108-13-3*
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Purity	Not provided
Method	
Method/Guideline followed	Similar to OECD Guideline 403
Test Type	Acute Inhalation toxicity (1 and 4 hour exposure intervals)
GLP (Y/N)	N
Year (Study Performed)	1976
Species/Strain	Rat/Strain not specified
Sex	Male
No. of animals/group	10
Vehicle	None
Route of administration	Vapor inhalation (Single 1 and 4 hour whole body exposure)
Exposure Concentrations (Actual analytical concentrations)	1 hour exposures: 0.108, 0.221, 0.264 and 0.309 mg/L 4 hour exposures: 0.047, 0.054, 0.070, 0.087 and 0.100 mg/L
Control group	No
Chamber analysis	Yes
Remarks field for test conditions	Eight groups of 10 rats/group were exposed for 1 (4 groups) or 4 hours (4 groups) to the test material as a vapor. The vapor generator consisted of a syringe drive, which fed the test material into a vaporization flask. Compressed heated nitrogen metered at a constant flow rate of 10 L/minute entered the vaporization flask, which was heated with a heating mantle. Both 1 and 4 hour exposures were conducted in a 300-liter stainless steel exposure chamber. The chamber was operated at a flow rate of 200L/minute. Actual chamber vapor concentrations were determined by infrared spectrophotometry. Animals were held for a 14-day post exposure observation period. Animal observations for toxicological signs and mortality were recorded daily. Individual body weights were recorded on Day 1 (immediately prior to exposure) and on Days 7 and 14. All animals were subjected to a gross necropsy.
Results	LC50 (1 hour) 0.247 mg/L (males) (95% confidence limits 0.229-0.271 mg/L) LC50 (4 hour) 0.076 mg/L (males) (95% confidence limits 0.067-0.087 mg/L)
Remarks	Decreased activity and conjunctivitis were observed during exposures. Decreased activity, labored breathing and conjunctivitis were observed during the post exposure observation periods. These observations were noted from 1 to 4 days post exposure after which the surviving animals were unremarkable. Deaths were observed through post exposure days 4 and 3 for the 1 and 4-hour

	exposure groups respectively. Mortality was as follows: Exposure Concentration (mg/L) / Exposure Duration (Hour) / Mortality (%) 0.108 / 1 / 0 0.221 / 1 / 10 0.264 / 1 / 80 0.309 / 1 / 100 0.047 / 4 / 0 0.054 / 4 / 10 0.070 / 4 / 30 0.087 / 4 / 70 0.100 / 4 / 100 Animals exposed for 4 hours at a concentration of 0.047 mg/L exhibited some weight gain during week one post exposure and normal weight gain by day 14-post exposure. All of the other surviving animals exposed for 1 or 4 hours lost or failed to gain weight during the first week of the post exposure period. Weight gain resumed in these animals by Day 14 post-exposure. Animals surviving the 1-hour exposure and sacrificed on day 14 post exposure exhibited a moderate incidence of focal areas of hemorrhage in the lungs. A slight incidence of this finding was observed in the 4-hour exposure surviving animals. LC50s, calculated according to the method of Litchfield and Wilcoxon, were as follows: LC50 (1 hour) 0.247 mg/L (males) (95% confidence limits 0.229-0.271 mg/L) LC50 (4 hour) 0.076 mg/L (males) (95% confidence limits 0.067-0.087 mg/L)
Conclusions	Following 1 or 4-hour whole body inhalation exposure to a vapor of the test material the 1 and 4 hour LC50s in male rats were as follows: LC50 (1 hour) 0.247 mg/L (males) (95% confidence limits 0.229-0.271 mg/L) LC50 (4 hour) 0.076 mg/L (males) (95% confidence limits 0.067-0.087 mg/L).
Data Quality	Reliable without restriction (Klimisch Code)
References	Unpublished confidential business information
Other	Updated: 7/21/2003

3.1.3 Acute Dermal Toxicity

Robust Summary 19-Dermal-1

NOTE: 4 dermal LD50s are available on this material with a range of 140-795 mg/kg

Test Substance	
CAS #	CAS# 12108-13-3
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Remarks	Test material dosed as received, purity not provided.
Method	
Method/Guideline followed	Similar to OECD Guideline 402
Test Type	Acute dermal toxicity
GLP (Y/N)	N
Year (Study Performed)	1975
Species/Strain	Rabbits/New Zealand White
Sex	Males and Females
No. of animals/group	4 (2 abraded, 2 intact)/dose level
Vehicle	None
Route of administration	Dermal
Dose level	112, 126, 141 and 158 mg/kg
Dose volume	Not provided.
Control group included	No
Range find study	Yes
Remarks field for test conditions	This study was conducted prior to the development of Test Guideline 402. This study deviated from Guideline 402 in that the skin of 2 of 4 treated animals/group was abraded prior to dosing. In addition the guideline calls for the evaluation of males and females using at least one dose level. These deviations were not considered sufficient to change the outcome of the study. Immediately prior to topical application of the test material, the hair of the upper back of each animal was closely clipped. The skin of two of the four treated animals/dose level was abraded prior to test material administration. A single administration of each dose level of the undiluted test material was administered dermally to four animals (2 abraded, 2 nonabraded)/group. The test material was kept in contact with the skin for a period of 24 consecutive hours under an impervious bandage. Test article was not removed. The animals were observed for 14 days after treatment. The dose site was evaluated daily for erythema and edema. Body weights were recorded on Days 0, 3, 7, 10 and 14. Animals were examined daily for illness or mortality. All animals were euthanized at the conclusion of the observation period. Gross necropsies were performed for all animals. The LD50 was calculated according to the method of Litchfield and Wilcoxon.
Results	LD50 = 140 mg/kg (122-159 mg/kg)
Remarks	The animal's general appearance and behavior were unremarkable.

	Mortality was as follows: Dose Level (mg/kg) — Mortality 112 — 0/4 126 — 1 (abraded)/4 141 — 2 (1 abraded, 1 intact)/4 158 — 3 (1 abraded, 2 intact)//4 All deaths occurred within 72 hours of dosing. Slight erythema and moderate edema were noted 24 hours post dosing in all dose groups. A dose response was not evident. These findings generally subsided in 1 to 3 days. Body weights were not adversely affected in those animals surviving to day 14. At necropsy evidence of congestion or possible internal hemorrhage were present in the major organs. Blood tinged urine was noted in one high dose animal.
Conclusions	The test article, when administered dermally as received to abraded and intact New Zealand white rabbits had an acute dermal LD50 of 140 mg/kg (122-159 mg/kg).
Data Quality	Reliable without restriction (Klimisch Code).
References	Unpublished confidential business information
Other	Updated: 7/23/2003

Robust Summary 19-Dermal-2

NOTE: 4 dermal LD50s are available on this material with a range of 140-795 mg/kg

Test Substance	
CAS #	CAS# 12108-13-3
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Remarks	Test material dosed as received, purity not provided.
Method	
Method/Guideline followed	Similar to OECD Guideline 402
Test Type	Acute dermal toxicity
GLP (Y/N)	N
Year (Study Performed)	1976
Species/Strain	Rabbits/New Zealand White
Sex	Males and Females
No. of animals/group	4 (2 abraded, 2 intact)/dose level
Vehicle	None
Route of administration	Dermal
Dose level	502, 795, 1260 and 2000 mg/kg
Dose volume	Not provided.
Control group included	No
Range find study	Yes
Remarks field for test conditions	This study was conducted prior to the development of Test Guideline 402. This study deviated from Guideline 402 in that the skin of 2 of 4 treated animals/group was abraded prior to dosing. In addition the guideline calls for the evaluation of males and females using at least one dose level. These deviations were not considered sufficient to change the outcome of the study. Immediately prior to topical application of the test material, the hair of the upper back of each animal was closely clipped. The skin of two of the four treated animals/dose level was abraded prior to test material administration. A single administration of each dose level of the undiluted test material was administered dermally to four animals (2 abraded, 2 nonabraded)/group. The test material was kept in contact with the skin for a period of 24 consecutive hours under an impervious bandage. Test article was removed by water wash. The animals were observed for 14 days after treatment. The dose site was evaluated daily for erythema and edema. Body weights were recorded on Days 0, 3, 7, 10 and 14. Animals were examined daily for illness or mortality. All animals were euthanized at the conclusion of the observation period. Gross necropsies were performed for all animals. The LD50 was calculated according to the method of Litchfield and Wilcoxon.
Results	LD50 = 795 mg/kg (568-1113 mg/kg)
Remarks	The animal's general appearance and behavior were unremarkable.

	Mortality was as follows: Dose Level (mg/kg) — Mortality 502 — 1(1 abraded) /4 795 — 2 (1 abraded, 1intact) /4 1260 — 3 (1 abraded, 2 intact) /4 2000 — 4 (2 abraded, 2 intact) /4 All deaths occurred within 24 hours and up to 6 days of dosing. Slight to well defined erythema and slight edema were noted within 24 hours post dosing in all dose groups. A dose response was not evident. These findings generally subsided within 3 days. Surviving animals exhibited a slight weight loss at day 3 but most recovered by day 7 and exhibited slight weight gain by day 14. At necropsy evidence of internal hemorrhage was present particularly of the kidney at dose levels of 795, 1260 and 2000 mg/kg. Animals at 502 mg/kg were unremarkable at necropsy.
Conclusions	The test article, when administered dermally as received to abraded and intact New Zealand white rabbits had an acute dermal LD50 of 795 mg/kg (568-1113 mg/kg).
Data Quality	Reliable without restriction (Klimisch Code).
References	Unpublished confidential business information
Other	Updated: 7/23/2003

Robust Summary-19-Dermal-3

NOTE: 4 dermal LD50s are available on this material with a range of 140-795 mg/kg

Test Substance	
CAS #	CAS# 12108-13-3
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Remarks	Test material dosed as received, purity not provided.
Method	
Method/Guideline followed	Similar to OECD Guideline 402
Test Type	Acute dermal toxicity
GLP (Y/N)	N
Year (Study Performed)	1976
Species/Strain	Rabbits/New Zealand White
Sex	Males and Females
No. of animals/group	4 /dose level
Vehicle	None
Route of administration	Dermal
Dose level	250, 350, 500 and 710 mg/kg
Dose volume	Not provided.
Control group included	No
Range find study	No
Remarks field for test conditions	This study was conducted prior to the development of Test Guideline 402. This study deviated from Guideline 402 in that the skin of 2 of 4 treated animals/group was abraded prior to dosing. In addition the guideline calls for the evaluation of males and females using at least one dose level. These deviations were not considered sufficient to change the outcome of the study. Twenty-four hours prior to topical application of the test material, the hair of the upper back of each animal was closely clipped. The skin of two of four animal/dose level was abraded prior to test material administration. A single administration of each dose level of the undiluted test material was administered dermally to four animals (2 abraded, 2 nonabraded)/group. The test material was kept in contact with the skin for a period of 24 consecutive hours under impervious plastic sheeting. Following 24 hours of exposure the sleeves were removed and observations were made for erythema, edema and eschar formation. The exposed area was wiped free of test material. Collars were used throughout the study to prevent ingestion. The animals were observed for 14 days after treatment. Body weights were recorded on Days 0 and 14. Animals were examined daily. All animals were euthanized at the conclusion of the observation period. Gross necropsies were performed for all animals. The LD50 was calculated according to the method of Miller, Lloyd and Tainter.
Results	LD50 = 420 mg/kg (170-670 mg/kg)
Remarks	During the first 24 hours convulsions were noted in one animal at the

	high dose and in two animals at 500 mg/kg. Ataxia was noted in one animal at 250 mg/kg and in two animals at 500 mg/kg. Hypoactivity was noted in two animals at both 350 and 500 mg/kg. Mortality was as follows: Dose Level (mg/kg) — Mortality 250 — 1(1 intact) /4 350 — 2 (1 abraded, 1intact) /4 500 — 2 (1 abraded, 1intact) /4 710 — 3 (1 abraded, 2intact) /4 All deaths occurred within 24 hours and up to 11 days of dosing. Slight to well defined erythema and slight edema were noted within 24 hours post dosing in some or all animals in all dose groups. A dose response was not evident. Surviving animals exhibited a slight weight loss at day 14. At necropsy evidence of lung consolidation, red spots in the intestine, red spots on the lung and nasal discharge were observed. No necropsy findings were noted at 250 mg/kg.
Conclusions	The test article, when administered dermally as received to abraded and intact New Zealand white rabbits had an acute dermal LD50 of 420 mg/kg (170-670 mg/kg).
Data Quality	Reliable without restriction (Klimisch Code).
References	Unpublished confidential business information
Other	Updated: 7/23/2003

Robust Summary-19-Dermal-4
NOTE: 4 dermal LD50s are available on this material with a range of 140-795 mg/kg

Test Substance	
CAS #	CAS# 12108-13-3
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Remarks	Test material dosed as received, purity not provided.
Method	
Method/Guideline followed	Similar to OECD Guideline 402
Test Type	Acute dermal toxicity
GLP (Y/N)	N
Year (Study Performed)	1976
Species/Strain	Rabbits/New Zealand White
Sex	Males and females
No. of animals/group	4 (1 male and 1 female abraded, 1 male and 1 female intact)/dose level
Vehicle	None
Route of administration	Dermal
Dose level	118.5, 177.8, 266.7, 400 and 2000 mg/kg
Dose volume	Not provided.
Control group included	No
Range find study	No
Remarks field for test conditions	This study was conducted prior to the development of Test Guideline 402. This study deviated from Guideline 402 in that the skin of 2 of 4 treated animals/group was abraded prior to dosing. This deviation was not considered sufficient to change the outcome of the study. Twenty-four hours prior to topical application of the test material, the hair of the upper back of each animal was closely clipped. The skin of one male and one female treated animal/dose level was abraded prior to test material administration. A single administration of each dose level of the undiluted test material was administered dermally to four animals (2 abraded, 2 nonabraded)/group. The test material was kept in contact with the skin for a period of 24 consecutive hours under impervious plastic sheeting. Following 24 hours of exposure the sleeves were removed, residual test material removed and observations were made for irritation. Collars were used throughout the study to prevent ingestion. The animals were observed for 14 days after treatment. Body weights were recorded on Days 0, 7 and 14. Animals were examined daily. All animals were euthanized at the conclusion of the observation period. Gross necropsies were performed for all animals. The LD50 was calculated according to the method of Weil and Thompson.
Results	LD50 = 196.7 mg/kg $\pm$ 37.46
Remarks	Excitation, tremors and convulsions were exhibited at 2000 mg/kg within 15 minutes of dosing. These symptoms lasted until death

	occurred. Excitation was also observed at 400 mg/kg within 20 minutes of dosing with recovery within one hour. One animal exhibited a slight body weight loss during week 1 and regained some weight during week 2. The test material was moderately irritating. Well-defined erythema and moderate edema were evident at 24 hours post dosing. Moderate desquamation was noted at 7 and 14 days post dosing. Mortality was as follows: Dose Level (mg/kg) — Mortality 119 — 0/4 178 — 2 (1 abraded, 1intact) /4 267 — 3 (2 abraded, 1intact) /4 400 — 4 (2 abraded, 2 intact) /4 2000 — 4 (2 abraded, 2 intact) /4 All deaths occurred within 1.5 hours and up to 4 days of dosing. All high dose animals died on day 1. At necropsy evidence of lung hemorrhage was present in the high dose early death animals. Pulmonary edema and, lung discoloration were evident in the animals that survived to study termination.
Conclusions	The test article, when administered dermally as received to abraded and intact New Zealand white rabbits had an acute dermal LD50 of 196.7 mg/kg $\pm$ 37.46.
Data Quality	Reliable without restriction (Klimisch Code).
References	Unpublished confidential business information
Other	Updated: 7/23/2003

Robust Summary 19-Dermal-4

NOTE: 4 dermal LD50s are available on this material with a range of 140-795 mg/kg

Test Substance	
CAS #	CAS# 12108-13-3
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Remarks	Test material dosed as received, purity not provided.
Method	
Method/Guideline followed	Similar to OECD Guideline 402
Test Type	Acute dermal toxicity
GLP (Y/N)	N
Year (Study Performed)	1976
Species/Strain	Rabbits/New Zealand White
Sex	Males and females
No. of animals/group	4 (1 male and 1 female abraded, 1 male and 1 female intact)/dose level
Vehicle	None
Route of administration	Dermal
Dose level	118.5, 177.8, 266.7, 400 and 2000 mg/kg
Dose volume	Not provided.
Control group included	No
Range find study	No
Remarks field for test conditions	This study was conducted prior to the development of Test Guideline 402. This study deviated from Guideline 402 in that the skin of 2 of 4 treated animals/group was abraded prior to dosing. This deviation was not considered sufficient to change the outcome of the study. Twenty-four hours prior to topical application of the test material, the hair of the upper back of each animal was closely clipped. The skin of one male and one female treated animal/dose level was abraded prior to test material administration. A single administration of each dose level of the undiluted test material was administered dermally to four animals (2 abraded, 2 nonabraded)/group. The test material was kept in contact with the skin for a period of 24 consecutive hours under impervious plastic sheeting. Following 24 hours of exposure the sleeves were removed, residual test material removed and observations were made for irritation. Collars were used throughout the study to prevent ingestion. The animals were observed for 14 days after treatment. Body weights were recorded on Days 0, 7 and 14. Animals were examined daily. All animals were euthanized at the conclusion of the observation period. Gross necropsies were performed for all animals. The LD50 was calculated according to the method of Weil and Thompson.
Results	LD50 = 196.7 mg/kg $\pm$ 37.46
Remarks	Excitation, tremors and convulsions were exhibited at 2000 mg/kg within 15 minutes of dosing. These symptoms lasted until death occurred. Excitation was also observed at 400 mg/kg within 20

	minutes of dosing with recovery within one hour. One animal exhibited a slight body weight loss during week 1 and regained some weight during week 2. The test material was moderately irritating. Well-defined erythema and moderate edema were evident at 24 hours post dosing. Moderate desquamation was noted at 7 and 14 days post dosing. Mortality was as follows: Dose Level (mg/kg) — Mortality 119 — 0/4 178 — 2 (1 abraded, 1intact) /4 267 — 3 (2 abraded, 1intact) /4 400 — 4 (2 abraded, 2 intact) /4 2000 — 4 (2 abraded, 2 intact) /4 All deaths occurred within 1.5 hours and up to 4 days of dosing. All high dose animals died on day 1. At necropsy evidence of lung hemorrhage was present in the high dose early death animals. Pulmonary edema and lung discoloration were evident in the animals that survived to study termination.
Conclusions	The test article, when administered dermally as received to abraded and intact New Zealand white rabbits had an acute dermal LD50 of 196.7 mg/kg ± 37.46.
Data Quality	Reliable without restriction (Klimisch Code).
References	Unpublished confidential business information
Other	Updated: 7/23/2003

3.2 Repeated Dose Toxicity

Robust Summary 19-RepeatedDose-1

Test Substance	
CAS #	CAS# 12108-13-3
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Remarks	Test material purity not provided
Method	
Method/Guideline followed	Non regulatory study
Test Type	A 14 week inhalation toxicity study in rats, mice and primates
GLP (Y/N)	Not specified
Year (Study Performed)	1978
Species: Strain	Rat: Sprague Dawley Mouse: Swiss Webster Primate: Cynomolgus
Route of administration	Vapor inhalation, whole body exposure
Duration of exposure	6 hours/day
Frequency of treatment	5 days/week for 14 weeks
Exposure concentration levels	0, 0.3, 3.5, 30.2 ug/L (Mean analytical concentration)
Sex	Rat: Male/Female Mouse: Male/Female Primate: Male only
Control and treatment groups	Rat: 10/sex/group Mouse: 10/sex/group Primate: 6 males/group
Post exposure recovery period	14 days primates only
Statistical methods	Body weight, hematology and clinical chemistry parameters, organ weights and organ/body weight ratios were analyzed. Mean values of all dose groups were compared to control at each time interval. Tests included parametric ANOVA with a Dunnett's test.
Dose rangefinding study	No
Remarks field for test conditions	Treated animals were exposed to the test material as a vapor in 6 m^3 stainless steel and glass exposure chambers. The low level vapor was generated using a 25 mL midget bubbler with a 145-175 micron porosity glass frit with an airflow of 0.3-0.6 L/minute. The mid and high-level generators consisted of a syringe pump connected to a counter current vaporizer packed with 4 mm glass beads and fitted with a 300-watt quartz immersion heater. Heated delivery lines were connected to each chamber. Chamber concentration was adjusted as a function of test material flow rate and chamber airflow. The generators were protected from light. Control animals were exposed to room air only. Chamber exposure concentrations were measured using a single 4 to 6 hour integrated

adsorption sample/chamber. Adsorption tubes were packed with Chromosorb 102. Samples were eluted with hexane and analyzed by infrared spectrophotometry.

Animal observations for toxicological signs and mortality were recorded daily. Individual body weights were recorded prior to exposure, twice weekly during the first two weeks and once weekly thereafter. Hematology evaluations were performed on 5 rats/sex/group and on all primates at 6 and 14 weeks of exposure. Clinical chemistry determinations were performed on 5 rats/sex/group at 14 weeks. Calcium and phosphorous determinations were performed on 5 rats/sex/group and on all primates at 14 weeks. Urinalysis was performed on 5 rats/sex/group and on all primates after 14 weeks of exposure and on 3 primates/group after 2, 4 and 8 days of recovery.

After 14 weeks of exposure all rats, mice and 3 primates/group were sacrificed and necropsied. Rats were fasted prior to necropsy. At 14 days post exposure the remaining primates were sacrificed and examined at necropsy. Weights were obtained for the heart, liver, kidney, testis, spleen, brain lung and trachea. Selected organs were examined microscopically for all primates and for 5 rats and mice/sex from the control and high exposure groups.

Results

Remarks

Mean analytical exposure concentrations over the duration of the study were 0.3, 3.5 and 30.2 ug/L in the low, mid and high exposure groups. Animals received a total of 68 exposures over a period of 14 weeks. Mortality over the duration of the study was as follows:

Number of Deaths/Total Number Available

Group	Rat		Mouse		Primate
	Male	Female	Male	Female	Male
Control	0/10	0/10	1/10	1/10	0/6
Low	0/10	0/10	0/10	1/10	0/6
Mid	0/10	3/10	2/10	0/10	0/6
High	1/10	2/10	2/10*	5/10*	0/6

*High exposure level mouse group terminated at week five due to significant toxicity.

High-level male and female rats and mice exhibited significant body weight decreases during the first two weeks of study. This finding was most pronounced in the mice and contributed to the early termination of the mice in the high level group. In the high-level rats body weights continued to be reduced compared to control throughout the study. At the mid exposure level female and male mice began to exhibit decreased body weights at week 3 and 14 respectively. Primate body weights were unremarkable.

The high exposure level rats and mice presented the most severe clinical signs of toxicity including rough coat, lethargy, dyspnea and death. The high exposure mice were terminated at week 5 due to the

severity of the observed toxicity.

No exposure related hematology effects were noted in any species. Clinical chemistry evaluations indicated an exposure related increase In blood urea nitrogen in the male and female rats in all exposed groups. In addition serum alkaline phosphatase was slightly elevated in the male and female rats at the high level only.

Group (Rat)	Mean BUN (mg/dL)		Mean Alkaline Phosphatase (mU/mL)	
	Male	Female	Male	Female
Control	16	14	16.9	128
Low	21*	26*	18.4	131
Mid	23*	26*	22.2	132
High	23*	24*	35.1*	184

* p=0.05

Calcium and phosphorous determinations were unremarkable in the male primates. Urinalysis in primates revealed an increased incidence of high-level animals with +1 ketones as compared to the controls (5 of 6 vs 1 of 6) at 14 weeks of exposure. No effect on urinary ketones was noted in the low or mid exposure levels.

Mean kidney weights were elevated in the mid level male and female mice. Liver weights were elevated in the low and mid exposure female mice only. Decreases in spleen and gonad weights were seen in the high exposure females at their early (week 5) termination. No organ weight effects were noted in the primates.

The high exposure male and female rats and mice exhibited treatment related microscopic alterations in the lungs. In the rats these alterations were characterized by an increase in the number of alveolar macrophages. These macrophages were generally present in the lumen of the alveoli adjacent to the terminal airway and contained finely granular brown material in their cytoplasm. A few animals exhibited focal pneumonitis. In the mice these alterations were characterized by varying degrees of bronchial epithelial hyperplasia, bronchial squamous metaplasia, bronchial epithelial erosion and in several cases bronchial wall fibrosis. In the primates, slight to moderate vacuolation was present in the white matter of the brain stem and cerebellar folia in 5 of 6 high level animals. This finding was present to a minimal degree in 3 of 6 control, 2 of 6 low level and 3 of 6 mid level primates. No pulmonary findings were of note in the primates.

Based on the results of this study, the Study Director concluded that the mouse was the species most sensitive to vapor inhalation exposure to this test material followed by the rat and monkey respectively. In addition female rodents appeared to be more sensitive then male

	rodents.
Conclusions	Under the conditions of this study, vapor inhalation exposure to this test material resulted in significant toxicity at the mid and high exposure levels. A NOAEL of 0.3 ug/L was selected for this study, by this reviewer, based on the increased blood urea nitrogen levels observed in rats at all exposure levels. Based on the results of this study, the Study Director concluded that the mouse was the species most sensitive to vapor inhalation exposure to this test material followed by the rat and monkey respectively. In addition female rodents appeared to be more sensitive then male rodents.
Data Quality	Reliable with restriction (Klimisch Code). Restriction due to the lack of microscopic data on the lungs of rodents in the low and mid exposure levels.
References	Unpublished confidential business information
Other	Updated: 7/24/2003

3.3 Developmental Toxicity :

Robust Summary 19-Devel-1

Test Substance	
CAS #	CAS# 12108-13-3
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Remarks	Test material purity not provided.
Method	
Method/Guideline followed	Similar to OECD 414
Test Type	Teratology Study in Rats
GLP (Y/N)	Y
Year (Study Performed)	1979
Species	Rat
Strain/Age	Sprague-Dawley CD, Approximately 10 weeks of age at receipt, 15 weeks of age at mating
Route of administration	Orally by gastric intubation
Duration of treatment	Fo males- Untreated Fo females- Treated from gestation day 6 through 15
Doses/concentration levels	0, 2.0, 4.5, 6.5 and 9.0 mg/kg/day
Vehicle control	Mazola® Corn Oil
Chemical Analysis of dosing solutions	No
Dose volume	7 mL/kg
Sex	Males and Females
Frequency of treatment	Females only, once/day, treated from gestation day 6 through 15
Analytical confirmation of concentration.	Yes
Control and treatment groups	25 Fo female rats/group
Post exposure observation period	None
Mating ratio	One male to one female
Duration of mating period	Untreated males and females were co-habitated (1:1) in order to provide the necessary number of mated females. Co-habitation was continuous until a copulatory plug was observed. This day was considered day 0 of gestation. Mated females were then sorted into the control and treated groups and housed individually.
Statistical methods	All statistical analysis compared treated groups to control. The litter was the unit of treatment. The incidence of maternal deaths, pregnant dams, early resorptions and post implantation loss were compared using the Chi-square test with Yates correction and/or Fisher's exact test. The incidence of fetuses and litters with malformations were compared by the Wilcoxon test. Maternal body weights, fetal body weights, fetal crown rump distances and maternal liver weights were compared by ANOVA, t-test and Dunnett's multiple comparison

	methods.
Remarks field for test conditions	Fo males and females were mated 1:1. Fo females were treated from gestation days 6 through 15. All females were examined daily for appearance and behavior. Female body weights were recorded on days 0, 6, 9, 12, 16 and 20 of gestation. Positive evidence of mating was confirmed by the presence of a vaginal copulatory plug (day 0 of gestation). All of the surviving Fo females were sacrificed on day 20 of gestation. The following parameters were evaluated: uterine weight, the location of viable and nonviable fetuses, early and late resorptions, number of total implantations and corpora lutea and maternal liver weights. The abdominal and thoracic cavities of the dams were examined and he carcasses were discarded. All fetuses were given a gross examination for external malformations and variations. The sex of each fetus was noted externally. Approximately one-third of the fetuses in each litter were placed in Bouin's fixative for subsequent visceral examination according to the Wilson procedure. The remaining fetuses in all litters were processed for staining of ossified skeletal structures using an Alizarin Red S staining procedure.

Results	One high dose female (9 mg/kg/day) was found dead on day 11 of gestation. This death was attributed to pneumonia. No deaths occurred in the control, low or mid dose animals. The surviving high dose animals exhibited a slight increase in the incidence of matting and staining of the anogenital fur. One 4.5 mg/kg/day animal was found to have a subcutaneous mass at cesarean section. This mass was determined to be a mammary adenocarcinoma. This was not considered treatment related, as it was found only 14 days after the initiation of test article administration. Reduced mean maternal body weight gain over the entire gestation period was noted in all of the treated groups compared to control. In addition the 6.5 mg/kg/day group exhibited a moderate reduction in mean body weight gain from days 6-9 of gestation and a mean weight loss during this interval. The 9 mg/kg/day group exhibited a statistically significant reduction in maternal body weight on day 9 of gestation. This resulted in a moderate reduction in mean maternal body weight gain over the entire gestation interval in the two highest dose groups. None of these differences from control were statistically significant with the exception day 9 in the high dose group. Mean maternal liver weights were unremarkable when compared to control. No treatment related differences from control were noted for the mean number of early resorptions, post implantation loss, mean number of viable fetuses, total implantations, corpora lutea, fetal sex distribution or fetal crown-rump distance. An increase in the incidence of malformations was noted at all dose levels, exclusively due to the presence of bent ribs at all dose levels compared to control. Bent ribs are not considered a malformation in the usual sense and when present with the exclusion of other malformations, as demonstrated in this study is not considered a developmental effect. In summary maternal toxicity was observed at the high dose level as evidenced by anogenital staining and maternal weight loss early in the treatment period. A slight reduction in mean fetal body weights and a slight to moderate reduction in mean maternal body weight over the entire gestation period were noted at all treatment dose levels. No significant developmental malformations were observed.
Conclusions	The Study Director concluded that maternal toxicity was observed at 9 mg/kg. Developmental toxicity was not observed.
Data Quality	Reliable with restriction (Klimisch Code). Restriction due to the lack of dosing solution analysis.
References	Unpublished confidential business information
Other	Updated 8/25/2003

3.4 Genetic Toxicity:

Robust Summary 19-Gentox-1

Test Substance	
CAS #	12108-13-3
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Remarks	Test material purity not provided.
Method	
Method/Guideline followed	Similar to OECD Guideline 471
Test Type	Bacterial Reverse Mutation Assay
GLP (Y/N)	Not specified
Year (Study Performed)	1977
Test System	*Salmonella typhimurium*
Strains Tested	*Salmonella typhimurium* tester strains TA98, TA100, TA1535, TA1537, TA1538
Exposure Method	Plate incorporation
Test Substance Doses/concentration levels	1, 10, 50, 100, 500, 1000 and 5000 ug/plate with and without activation
Metabolic Activation	With and without (S9 fraction mix of livers of Aroclor 1254 pretreated rats)
Vehicle	Not specified
Tester strain, activation status, Positive Controls and concentration level	TA98 +S9 2-anthramine 2.5 ug/plate TA98 -S9 None - TA100 +S9 2-anthramine 2.5 ug/plate TA100 -S9 None - TA1535 +S9 2-anthramine 2.5 ug/plate TA1535 -S9 B-propiolactone 10 ug/plate TA1537 +S9 2-anthramine 2.5 ug/plate TA1537 -S9 9-aminoacridine 100 ug/plate TA1538 +S9 2-anthramine 10 ug/plate TA1538 -S9 2-nitrofluorene 5 ug/plate
Vehicle Control	Not specified
Statistical Analysis	No
Dose Rangefinding Study	No
S9 Optimization Study	No
Remarks field for test conditions	This study was conducted prior to the development of OECD Guideline No. 471. This study deviates from the guideline in that Tester Strain TA 1538 is not called for in the guideline but it was included. In addition E. coli WP2 urvA Tester Strain called for in the guideline was not included. There were two treatment sets for each tester strain, with (+S9) and without (-S9) metabolic activation. Each of the tester strains was dosed with seven concentrations of test substance, vehicle control (unspecified), and a positive control. Multiple plates (number unspecified)/dose group/strain/treatment set were evaluated. Up to 50 ul of test material, positive control or vehicle control were added to

	each plate along with 0.05 mL of tester strain, S9 mix (if needed) and 2 mL of top agar. This was overlaid onto the surface of minimal bottom agar in a petri dish. Plates were incubated for 48 hours at 37°C. The numbers of revertant colonies were counted. Some of the revertants were routinely tested to confirm that they were his$^+$ and rfa$^-$. The test material was considered a mutagen if a dose related increase was found in the number of revertant colonies.
Results	The test substance was not genotoxic in this assay with or without metabolic activation.
Remarks	All data were acceptable and no positive, dose related, increases in the number of mean revertants/plate were observed with any of the tester strains with or without metabolic activation. Toxicity was observed in all strains at one or more dose levels as follows: TA98- 5000 ug/plate without activation TA100- 5000 ug/plate with activation TA1535- ≥500 ug/plate with and without activation TA1537- ≥500 ug/plate without activation TA1538- ≥1000 ug/plate without activation, ≥500 ug/plate with activation The positive control for each respective test strain exhibited an appropriate response (with or without S9) over the mean value of the vehicle (negative) control for a given strain, confirming the expected positive control response.
Conclusions	Under the conditions of this study, the test material was not mutagenic.
Data Quality	Reliable with restriction (Klimisch Code). Restriction due to the lack of specificity regarding: the selection of dose levels, identification of the vehicle and vehicle control and the number of plates/concentration evaluated during the study.
References	Unpublished confidential business information
Other	Updated: July 18, 2003

Robust Summary 19-Gentox-2

Test Substance	
CAS #	CAS# 12108-13-3
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Remarks	Test material purity not provided.
Method	
Method/Guideline followed	OECD Guideline 473
Test Type	*In Vitro* Chromosomal Aberration Assay in CHO Cells
GLP (Y/N)	Not Specified
Year (Study Performed)	1995
Test System	Chinese hamster ovary cells
Culture Preparation and Maintenance	Cells were cultured in Eagle MEM Medium containing 10% fetal bovine serum, 1% sodium pyruvate and 1% non-essential amino acids at 37^{o}C, in 5% CO_2 in air and high humidity.
Exposure Method	Dilution
Test Substance Doses/concentration levels	Sample concentrations of 0.01, 0.02 and 0.04 ul/mL were evaluated with and without metabolic activation.
Metabolic Activation	With and without S9 fraction mix of livers of Aroclor 1254 pretreated rats.
Vehicle	None
Positive Control Materials	0.05 mM methyl methanesulfonate without activation 25 ug/mL Cyclophosphamide with activation
Statistical Analysis	Statistical analysis performed using the chromosome aberration assay data management and analysis system software developed under contract to the U.S. EPA.
Remarks field for test conditions	Three trials were conducted. In the first trial, cells were treated for 3 hours, with and without metabolic activation. In trial 2 the cells were treated continuously without metabolic activation and for 3 hours with activation. The first two trials were performed using plastic tissue culture dishes. A third trial was performed with metabolic activation using glass plates treated with 1mM magnesium acetate to promote cell attachment. In trials using a 3-hour treatment period, the cells were washed three times with fresh medium, and then incubated in complete medium until harvested. In all trials, the cells were harvested 16 hours following the initiation of treatment using standard cytogenetics techniques. Slides were coded and scored blind to avoid observer bias. One hundred metaphase cells were analyzed from each of two cultures from each treatment set. For cultures in which the incidence of chromosomal aberrations was high, only 50 cells were analyzed.

Results	In the presence of metabolic activation the test material was associated with an increase in the percentage of cells that contained chromosome aberrations.
Remarks	Assay results were as follows: */** Statistically significant 0.05/0.01 The data suggest that exposure to the test material in the absence of metabolic activation did not cause an increase in the percentage of cells which contained chromosome aberrations. However in the presence of metabolic activation the test material was associated with an increase in the percentage of cells which contained chromosome aberrations. Positive and control group responses were as expected. The positive control groups have frequencies of aberrations outside the normal range of the control and at 14 times the control value.
Conclusions	In the presence of metabolic activation the test material was associated with an increase in the percentage of cells that contained chromosome aberrations.
Data Quality	Reliable without restriction (Klimisch Code)
References	Unpublished confidential business information
Other	Updated: 12/08/2003

Dose (uL/mL)	% Cells with Aberrations (3 Hour Exposure-Without Metabolic Activation)	% Cells with Aberrations (16 Hour Exposure-Without Metabolic Activation)	% Cells with Aberrations (3 Hour Exposure-With Metabolic Activation)	% Cells with Aberrations (3 Hour Exposure-With Metabolic Activation)
0	4	6.3	4.5	5.0
0.01	4.5	6.0	4.0	4.0
0.02	2.5	10.0	10.5*	14.5
0.04	5.6	8.0	45**	51**
Positive Control	100**	100**	65**	76**

Robust Summary 19-Gentox-3

Test Substance	
CAS #	CAS# 12108-13-3
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Remarks	Test material purity not provided.
Method	
Method/Guideline followed	OECD Guideline 474
Test Type	Mammalian Erythrocyte Micronucleus Test
GLP (Y/N)	Not Specified
Year (Study Performed)	1995
Species	Mouse
Strain	C57B1; 9 weeks of age at initiation of dosing
Route of administration	Intraperitoneal injection
Duration of test	Three treatment days followed by a 24-hour holding period.
Doses/concentration levels	0, 12.5, 25 or 50 mg/kg
Dose volume	0.1ml/10 grams of body weight
Sex	Males and females
Frequency of treatment	Three treatments administered approximately 24 hours apart.
Control and treatment groups	Olive oil vehicle control; Cyclophosphamide positive control: 45 mg/kg (in phosphate buffered saline), 12.5, 25 or 50 mg/kg
Statistical methods	Statistical analysis performed using the micronucleus assay data management and analysis system software developed under contract to the U.S. EPA.
Dose Rangefinding Study	Yes
Remarks field for test conditions	The animals from each group were sacrificed for bone marrow sampling 24 hours after the third dose. 2000 PCEs from each animal were examined for the presence of micronuclei. The percent of PCE in the total population of erythrocytes was determined for each animal by counting a total of 1000 polychromatic and normochromatic erythrocytes.
Results	
Remarks	The dose range finding assay indicated that doses over 50 mg/kg could cause animal deaths or distress. In the main study there were no dose related increases or statistical differences in micronuclei formation observed at any dose level. Cytotoxicity was not observed since there were no statistically significant decreases in the percentage of polychromatic erythrocytes compared to the vehicle control. The positive control induced a ten-fold increase in mean micronucleated PCEs in both sexes compared to the vehicle controls, which indicated the positive control was clastogenic and responded appropriately.

Conclusions	The test material was not genotoxic under the conditions of this study.
Data Quality	Reliable with restriction (Klimisch Code)
References	Unpublished confidential business information
Other	Updated: 12/9/2003

Robust Summary 19-Gentox-4

Test Substance	
CAS #	CAS# 12108-13-3
Chemical Name	Methylcyclopentadienyl manganese tricarbonyl
Remarks	Test material purity not provided.
Method	
Method/Guideline followed	OECD Guideline 474
Test Type	Mammalian Erythrocyte Micronucleus Test
GLP (Y/N)	Not Specified
Year (Study Performed)	1995
Species	Mouse
Strain	C57B1; 9 weeks of age at initiation of dosing
Route of administration	Intraperitoneal injection
Duration of test	One treatment day followed by a 24 and 48-hour holding periods.
Doses/concentration levels	0, 50, 75 or 100 mg/kg with 24 hour post dose holding period 0, 75 or 100 mg/kg with 48 hour post dose holding period
Dose volume	0.1ml/10 grams of body weight
Sex	Males and females
Frequency of treatment	Once/animal
Control and treatment groups	Olive oil vehicle control; Cyclophosphamide positive control: 25 mg/kg (in phosphate buffered saline), 0, 50, 75 or 100 mg/kg with 24 hour post dose holding period, 0, 75 or 100 mg/kg with 48 hour post dose holding period
Statistical methods	Statistical analysis performed using the micronucleus assay data management and analysis system software developed under contract to the U.S. EPA.
Dose Rangefinding Study	Yes
Remarks field for test conditions	The animals from each group were sacrificed for bone marrow sampling 24 hours or 48 hours after dosing. 2000 PCEs from each animal were examined for the presence of micronuclei. The percent of PCE in the total population of erythrocytes was determined for each animal by counting a total of 200 polychromatic and normochromatic erythrocytes.
Results	
Remarks	The dose range finding assay indicated that doses over 100 mg/kg could cause animal deaths. In the main study there were no dose related increases or statistical differences in micronuclei formation observed at any dose level. Cytotoxicity was evident in the male 48 hour groups as indicated by statistically significant decreases in the percent of polychromatic erythrocytes compared to the vehicle control. The positive control induced a statistically significant increase in mean micronucleated PCEs in both sexes compared to the vehicle controls, which indicated the positive control was clastogenic and responded appropriately.

Conclusions	The test material was not genotoxic under the conditions of this study.
Data Quality	Reliable with restriction (Klimisch Code)
References	Unpublished confidential business information
Other	Updated: 12/9/2003